Response

Claims 94-110, 112-113, and 115-116 are currently pending and under examination. Claims 94, 96, 101, 108, 112 and 113 have been amended to more clearly define Applicants' invention. The term "aqueous humor inflow" is supported at least at page 4 of the specification.

No new terms or new matter is added to any claim.

Response to Claim Rejection under 35 U.S.C. § 112, first paragraph.

The Examiner has rejected claims 94-104, 107-110, 112, 113, 115 and 116 under 35 U.S.C. §112, first paragraph, under the written description requirement regarding Applicants' use of the term "selective inhibitor" in claims 94 and 108. Although the Examiner states that there is not a question regarding the effectiveness of the inhibitors at low concentrations, the Examiner questions the support for the term "selective inhibitor," quoting pages 5 and 11 from the specification. Applicants argue that whether the exact term was used in the specification or not, the meaning is clear that the inhibitors operate as "selective inhibitors." Nevertheless to further the prosecution, Applicants have removed the term "selective inhibitor" from claims 94 and 108, and replacing the term with "an inhibitor."

The Examiner has maintained the rejection regarding Applicants' use of the term "precursor prostaglandins" in claim 101. In making this rejection, the Examiner appears to be concerned that the referenced latanoprost is not representative of the entire class of prostaglandin precursors. On the other hand, the exemplification using latanoprost does not exclude other members of the class since only "at least one compound selected from the group" is claimed. See Applicants' specification at page 3, lines 27-28. Latanoprost exemplifies "at least one compound" from the group . . . .precursor prostaglandins, thus satisfying the requirement under the law. However, in an effort to advance the claim to allowance, Applicants have now narrowed the class of precursor prostaglandins referenced in claim 101 to specifically "latanoprost-type precursor prostaglandins," which is in keeping with the purpose of §112, first paragraph to ensure that there is an adequate disclosure of the invention for which patent rights are sought and the purpose of the description requirement is to state what is needed to fulfill the enablement criteria, these requirements may be viewed separately but they are intertwined. *Kennecott Corp. v. Kyocera*

International, Inc., 5 USPQ2d 1194, 1197 (Fed. Cir. 1987) ("The written description must communicate that which is needed to enable the skilled artisan to make and use the claimed invention.") Although the specification does not state the word "type" with latanoprost, the courts have explained that "adequate description under the first paragraph of 35 U.S.C. §112 does not require literal support for the claimed invention. Rather, it is sufficient if the originally-filed disclosure would have conveyed to one of ordinary skill in the art that the appellant had possession of the concept of what is claimed." *Ex parte Parks*, 30 USPQ2d 1234, 1236 (BPAI 1993). Thus, Applicants have met the written description requirement by identifying the subset (type) of prostaglandins precursor drugs that are intended.

Accordingly, Applicants respectfully ask that the §112, first paragraph, rejection be reconsidered and withdrawn.

Response to Claim Rejection under 35 U.S.C. § 112, second paragraph.

The Examiner has rejected claims 94-104, 107-110, 112, 113, 115 and 116 under 35 U.S.C. §112, second paragraph, as indefinite. The Examiner has rejected Applicants' use of the term "very low" in claims 94 and 108, explaining that "very" is an indefinite term, absent further definition. Applicants argue that in the context in which it is used with regard to the concentration, the modifier "very low" is clear. Nevertheless, in an effort to further the prosecution, Applicants have removed the term "at very low concentrations" from claims 94 and 108.

In addition, the Examiner has rejected claims 96, 112 and 113 for the use of the term analogue with amiloride, stating that analogs (or in an alternative spelling analogues) are indefinite. The use of amiloride "analogues" is supported at least at page 15, line 3 and at Table 5. Nevertheless, in an effort to further the prosecution, Applicants have removed the term "analogs" from claims 96 and 112, which should eliminate the 112 rejection associated with those claims. Exemplified amilorides are now correctly listed in claims 107 and 113.

Accordingly, Applicants respectfully ask that the §112, second paragraph, rejection be reconsidered and withdrawn.

Response to First Rejection under 35 U.S.C. §102(b) over Cherksey

The Examiner has maintained the previous rejection of claims 94-96, 102 and 105-107 under 35 U.S.C. §102(b) as anticipated by Cherksey (US Patent No. 4,950,591). In making this rejection, the Examiner still relies upon Cherksey for the teaching that amiloride is an agent that "blocks ion transport and interacts with a Sodium-Hydrogen Exchange inhibitor," and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. See columns 1-3. This conclusion is incorrect. Cherksey does not actually teach any interaction with a "sodium-hydrogen exchange inhibitor," nor is the amiloride gel utilized by Cherksey at pH 4.5 suitable for actual administration to the eye.

As described in the first paragraph of Applicants' invention, as well as in the record, the formation of the aqueous humor requires active metabolism occurring within the double-layered ciliary epithelium, *i.e.*, two layers of cells whose apical membranes are juxtaposed (see Applicants' FIG. 1). The apex to apex positioning of the secretory epithelia is unusual. Thus, there is a layer of the outer pigmented epithelium (PE), with its basement membrane resting on the ciliary stroma, and the inner nonpigmented epithelium (NPE), with its basement membrane facing the posterior chamber. The secretion is based on the movement of water and electrolytes from the ciliary stroma across the epithelial cell layer, and into the posterior chamber, where they are secreted at the basolateral membrane as aqueous humor. See, Civan and Macknight, "The ins and outs of aqueous humour secretion," *Experimental Eye Research* 78(3):625-631 (March 2004) of record.

The secretion proceeds in three steps: stromal chloride entry into pigmented cells, diffusion through gap junctions and final non-pigmented cell secretion. At the stromal surface, swelling-and cyclic adenosine monophosphate-activated maxi-chloride channels can recycle chloride, reducing net chloride secretion. While at the aqueous-humor surface, swelling- and A3 adenosine receptor-activated chloride channels subserve chloride release into the aqueous humor. See, Do and Civan, "Swelling-activated chloride channels in aqueous humour formation: on the one side and the other," *Acta Physiologica* 187(1-2): 345-352 (May/June 2006) of record.

However, the epithelial sodium channel referred to by Cherksey, found in the NPE cell layer facing the aqueous humor, falls outside of Applicants' invention which is limited

to inhibition of the sodium-hydrogen antiports (or exchangers). The ciliary epithelial cell antiports are also known as exchangers or counter-transporters. The antiports of the present invention (FIG. 1) are the paired sodium-hydrogen (Na^+/H^+) and $Cl^-/HCO3^-$ antiports (or exchangers) in the pigmented epithelial (PE) cell layer. The formation of aqueous humor occurs as Na^+ enters the PE cells from the body side, and, in exchange, hydrogen ion (H^+) is released from the cell onto the body side.

As noted in Applicants' background of the invention, there are multiple, interacting causes of increased intraocular pressure, and affecting the general process by the use of inhibitors that are neither taught, nor suggested, in Applicants' invention, nor claimed by Applicants, would be impermissible. There is no evidence that the cited prior art affects or inhibits the sodium-hydrogen antiports, or that, in fact, Cherksey's method operates on the sodium-hydrogen antiports at all since there are many components to the control of intraocular pressure. Without evidence that Cherksey's gel would necessarily operate as Applicants' inhibition of NHE antiport activity, such a selective effect is not, and cannot be assumed to be, inherent in the Cherksey reference.

In response to the Examiner's conclusions, it is known that amiloride blocks the sodium channel – but that requires an understanding that the sodium channel is not the same as or equivalent to the sodium-hydrogen antiport. The sodium channel and the sodium-hydrogen antiports, as explained above – are not even found in the same regions of the epithelial cells of the eye. In fact, Merck developed amiloride for the purpose of blocking the sodium channel. However, while Cherksey claims the use of amiloride solely for the use of the isolated peptide as a diagnostic and experimental tool, whereas by comparison, Applicants' invention neither teaches, nor claims, a method for regulating the "sodium channel" or its role in aqueous humor formation. Cherksey's method of binding amiloride in affinity gels would affect only the sodium channels (including amiloride-sensitive NPE sodium channels) that underlie *reabsorption* of aqueous humor fluid – not the formation of the aqueous humor, meaning that by definition the Cherksey teachings fall outside of Applicants' invention.

Cherksey states an "understanding" at col. 1, lines 24-27 as background for his invention that "Amiloride is widely thought to interact with a Na^+/H^+ exchanger [antiport] at high concentrations and a Na^+ channel protein at much lower concentrations."

However, this statement cannot be read to include anything more than what is taught by Cherksey, *i.e.*, to find low concentrations of amiloride to test for sodium channels using affinity gels in a laboratory setting. The Examiner offers no motivation for assuming that Cherksey also intended to affect or inhibit the sodium-hydrogen channels, which would necessarily require much higher, in fact dangerously high, concentrations of amiloride. The basis for Cherksey's statement was solubility. The limited solubility of amiloride remained a problem ten years after Cherksey's patent, and is the reason that Avila *et al.*, "Inhibitors of NHE-1 Na^+/H^+ exchange reduce mouse intraocular pressure," *Invest. Ophthalmol. Vis. Sci.* 43:1897-1902 (2002) (previously cited in Applicants' record, not as prior art, but establish the state of the art) included the solvent DMSO (dimethylsulfoxide), see page 1899, paragraph 3. But even then, 10 mm concentrations of amiloride at the eye surface had no effect on intraocular pressure, presumably because the concentration reaching the NHE target was much lower. While there are pharmaceutical ways of increasing solubility, none have as yet been developed for amiloride.

Moreover, Cherksey teaches that blocking the sodium channel with amiloride *increases* inflow, *resulting in increased intraocular pressure* – which is contrary to the clinical intent of Applicants' invention. On the basis of that information, a knowledgeable practitioner would be led to *stimulate* the NPE sodium channels; not block them, and further demonstrates that Cherksey's invention to determine the effect of amiloride on the sodium channels would have had no effect, particularly at the concentrations used by Cherksey, on the sodium-hydrogen antiports that are selectively inhibited by Applicants' claimed method. Thus, Cherksey not only fails to anticipate Applicants' invention, it actually leads one away from what is taught by Applicants' patent application regarding regulation of the antiports.

Cherksey neither mentions, nor suggests, that inhibiting or blocking NHE exchange would reduce aqueous humor inflow or intraocular pressure. Thus, although Cherksey, as a valid patent, may be admitted for all that it teaches, it can at best be considered valid only for the use of amiloride, and at that only for the effect on sodium channels, it cannot be considered valid for that which it fails to encompass. Accordingly, Cherksey fails to anticipate each and every element of Applicants' claimed invention - which requires "selective inhibition of the sodium-hydrogen antiports" by the administration of a selective

inhibitor – the NHE inhibitor. As a result, the Cherksey reference fails to anticipate Applicants' present invention.

Applicants ask that in light of the arguments and evidence of record, and of the amended claims, the rejection of Applicants' claims under 35 U.S.C. §102(b) over Cherksey be reconsidered and withdrawn, and the case moved to allowance.

Response to Second Rejection under 35 U.S.C. §102(b) over Drug Facts and Comparisons

The Examiner has maintained the rejection of claims 94 and 102-105 under 35 U.S.C. §102(b) as being unpatentable under "Drug Facts and Comparisons" (1994). In making this rejection, the Examiner relies upon "Drug Facts and Comparisons" for teaching the use of timolol, which the Examiner defines as a beta blocker in reliance on the prior art and on Applicants' list at page 6, lines 23-26. However, as previously shown on the record, by cited prior art and by Declaration in Applicants' prior Response dated November 10, 2005, timolol was not recognized by those knowledgeable in the field to be a sodium-hydrogen exchange (NHE) inhibitor.

Regardless of the Examiner's arguments that reduction of intraocular pressure is demonstrated by the use of timolol in "Drug Facts and Comparisons," the reference offers no evidence that timolol achieved any inhibition of sodium-hydrogen antiport activity *in the ciliary epithelial cells*. It describes a change in intraocular pressure, not any effect what-so-ever on the ciliary epithelial cells.

Applicants not only "administer" a pharmaceutical composition in their claimed method, the composition is expressly an NHE inhibitor that inhibits "sodium-hydrogen antiport activity" in the ciliary epithelial cells. This further emphasizes that, while "Drug Facts and Comparisons" may say that a small reduction of intraocular pressure was noted in the subject animal, the cited art does not offer any treatments of antiport activity – yet regulating antiport activity is expressly Applicant's invention – not simply reducing intraocular pressure.

This is not a case of inherency because while "Drug Facts and Comparisons" may report a reduction of intraocular pressure in the subject animal in conjunction with treatment, there is no evidence provided in the rejection that would indicate that the noted slight reduction was *a selective result of inhibition or regulation of antiport activity* or that

the epithelial cells were even affected. The cited reference offers no suggestion that intraocular pressure was tested by the authors of "Drug Facts and Comparisons."

In citing *Continental Can*, the Office must look at the entire holding of the decision, which further explains that

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA Inc. v. Monsanto,* 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

It cannot be assumed, without some evidence supporting the conclusion that the treatment by the authors of "Drug Facts and Comparisons" "could" have regulated or altered the antiport activity, or that such action on the antiports was inherent based upon the limited disclosure in the cited reference. See, e.g., *Verdegaal Brothers, Inc. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) ("Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.).

Only Applicants' own invention regarding the method of therapeutically inhibiting NHE antiport activity in the ciliary epithelial cells of the eye of a subject could lead to the Examiner's stated conclusions based upon the treatment described in "Drug Facts and Comparisons," which refers only to reduction of pressure. It is impermissible to rely upon Applicants' own invention to teach what the Examiner says is shown in the prior art. Antiports are not mentioned once in the cited reference, thus absent some teaching that is not provided by the Examiner, it cannot simply be assumed that the use of timolol in the cited reference had any effect in the antiports – except by impermissible reliance on Applicants' own invention.

However, the Examiner also refers to the use of timolol in "Drug Facts and Comparisons" as "a protective utility," and states that limitations from the specification cannot be read into the claims. More specifically the Examiner refers to "Applicants' failure to distance the proffered claims from the anticipated **prophylactic** utility" of the cited reference.

Applicants specifically claim a **therapeutic** method, in both the preamble and body of the independent claims (upon which all remaining claims depend). *Prophylactic* administration would be, by common definition, *before* the onset of symptoms, *i.e.*, before the need arises. *Therapeutic* administration would *follow onset* of the need. Accordingly, Applicants' invention is necessarily therapeutic, rather than prophylactic as stated in the independent claims.

Consequently since each and every element of Applicants' claims 94 and 102-105 are not expressly or inherently described in a single prior art reference, Applicants' claims are not anticipated under 35 U.S.C. § 102(b). As a result, Applicants ask that in light of the claim amendments, the arguments of record and the foregoing arguments, that the rejection under 35 U.S.C. § 102(b) over "Drug Facts and Comparisons" be reconsidered and withdrawn, and the case moved to allowance.

Response to Rejections under 35 U.S.C. §103(a) over Adorante and Cherksey

The Examiner has maintained the rejection of claims 94-96, and 99 – 110, 112, and 113 under 35 U.S.C. §103(a) as unpatentable over Adorante (US Patent No. 5,559,151) and Cherksey (US Patent No. 4,950,591). In making this rejection, the Examiner relies on Adorante for the use of 4,4'-diisothiocyanato-stilbene-2,2'-disulfonate (DIDS) to treat glaucoma and/or ocular hypertension, although the Examiner agrees that Adorante fails to suggest co-administration of NHE/NHE1 inhibitors. However, the Examiner further combines Cherksey with Adorante for the teaching that amiloride blocks ion transport and interacts with a sodium-hydrogen exchange inhibitor and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. The Examiner's conclusion is based on the premise that it would have been obvious to "employ two agents well known to treat glaucoma/ocular hypertension together to treat the very same condition." However, Applicants refute the Examiner's conclusion.

Applicants neither teach, nor claim, treatment of glaucoma, nor ocular hypertension. Consequently, without making impermissible and unsupported assumptions, there is no basis for applying the cited combined prior art against Applicants' claimed invention. Adorante and Cherksey both refer only to blocking or inhibiting the chloride channels of the NPE cells, and therefore the combined reference can offer nothing more

than the sum of its components. The combined reference teaches only the use of chloride-channel blockers (Adorante uses DIDS; Cherksey uses an amiloride based gel) in NPE cells, without any reference what-so-ever to bicarbonate-chloride exchange. The chloride channel is not even shown in Applicants' Figures – because, as stated above and on the record, it is not part of Applicants' invention. Only inhibition of, and within, the NPE cells is claimed in Applicants' invention. The use of DIDS as a chloride-channel blocker is not Applicants' invention, nor is a treatment for intraocular pressure.

Applicants' invention offers no discussion regarding the "sodium channels" that are referenced by the Examiner regarding the combined references. This is because that subject matter fails outside of Applicants' present invention. Although Cherksey and Adorante have documented the use of sodium channel inhibitors and their effect on intraocular pressure, this is not Applicants' invention and it offers no suggestion of any element of Applicants' claimed invention. To the contrary, there is no basis in the cited combined art for the Examiner to assume that there is any teaching specific to Applicants' method for inhibiting the NHE antiports and control of NHE transport *within* and between the cited epithelial cells in the eye. Thus, Applicants' claimed methods – expressly specific to the use of NHE antiport inhibitors – are neither suggested by, nor inherent in, the combined prior art. There are clearly multiple major ionic mechanisms operating as a cause of unwanted increases in intraocular pressure, but to preclude inventions that address the other avenues involved in aqueous humor regulation, would impermissibly block future advances in the science.

Since combined Cherksey/Adorante fail to teach administering NHE/NHE1 inhibitors to the antiports to regulate antiport activity by selectively inhibiting sodium-proton exchange, the combined reference cannot render Applicants' invention obvious. Even when combined, the cited references fail to teach each and every element of Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 94-96, and 99-110, 112, 113 under 35 U.S.C. §103(a) be reconsidered and reversed, and the case move to allowance.

Response to Rejections under 35 U.S.C. §103(a) over Brandt and Cherksey

The Examiner has rejected claims 94-98, and 102 – 110, 112, and 113 under 35 U.S.C. §103(a) as unpatentable over Brandt (US Patent No. 5,559,151) and Cherksey (US

Patent No. 4,950,591). In making this rejection, the Examiner relies on Brandt for the use of an inhibitor of a Na^+-K^+-$2Cl^-$ (symport), such as bumetanide, to treat glaucoma and/or ocular hypertension, although the Examiner agrees that Brandt fails to suggest co-administration of NHE/NHE1 inhibitors. However, the Examiner further combines Cherksey with Brandt for the teaching that amiloride blocks ion transport and interacts with a sodium-hydrogen exchange inhibitor, and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. The Examiner's conclusion is based on the premise that it would have been obvious to "employ two agents well known to treat glaucoma/ocular hypertension together to treat the very same condition." Applicants, however, refute the Examiner's conclusion.

Applicants neither teach, nor claim, treatment of glaucoma, nor ocular hypertension. Consequently, without making impermissible and unsupported assumptions, there is no basis for applying the cited combined prior art against Applicants' claimed invention. Contrary to the Examiner's position, Applicants point out there are many different components recognized in the prior art to control intraocular pressure, and the identification of a method in the prior art that affects one part of this complex process in no way necessarily precludes the invention of another method of selectively controlling a completely different region of the eye.

Dr. Civan and others have demonstrated that bumetanide is, by itself, ineffective in lowering IOP *in vivo*. See, Tian *et al.* "Effects of Adenosine Agonists on Intraocular Pressure and Aqueous Humor Dynamics in Cynomolgus Monkeys," *Exp. Eye Res.* 64:979-989 (1997) of record (demonstrating that bumetanide had no effect on IOP of live monkeys). Subsequently, Dr. Civan and associates demonstrated that bumetanide also has no effect on IOP of the live mouse, and it lowers IOP only if the sodium-proton exchange is also blocked (see, 2002 Avila *et al.*, reference in *Invest. Ophthalmol. Vis. Sci.* 43:1897-1902) of record.

As a result, when the cited combined prior art is read in light of the state of the art, although Brandt's patent may teach that use of bumetanide to block the sodium-potassium-chloride co-transporter, it clearly offers no suggestion of Applicants' process directed to the selective inhibition of sodium-proton exchange. Thus, Brandt has no relevance to Applicants' claimed method of selectively blocking of sodium-proton exchange, as

confirmed by the Examiner's statement in the Office Action that Brandt "fails to suggest administration of selective NHE/NHE1 inhibitors." For the above stated reasons, Cherksey teaches modulation of the amiloride-sensitive sodium channel, but that is not Applicants' invention. In fact, Applicants' neither mention, nor consider, the role of the sodium channel in the instant patent application which focuses instead on regulation of the NHE antiport during aqueous humor formation.

Consequently, linking treatment of bumetanide as an inhibitor of a Na^+-K^+-$2Cl^-$ (symport) (Brandt) with amiloride in a gel to block the ENaC sodium channel (Cherksey) would in no way lead one of skill in the art to believe that the combined teaching could selectively block sodium-proton exchange (since that is not mentioned or suggested by either component of the combined art), in order to reduce net inflow at the sodium-hydrogen antiports within the ciliary epithelial cell layer. As a result, when the cited references are combined as proposed, the combination fails to teach each and every element of Applicants' claimed invention. Of course, as above, inherency does not apply to the combined references. See, *Jones v. Hardy* 220 USPQ 1020, 1025 (Fed. Cir. 1984) (The fact that a claimed invention is based on an inherent quality of a product well known in the art does not mean the invention is obvious, as this confuses anticipation by inherency with obviousness).

Since Cherksey fails to teach administering NHE/NHE1 inhibitors to the antiports, as taught for the first time by Applicants, Cherksey cannot supplement the gap left by Brandt. Neither teaches a method for therapeutically reducing net inflow by inhibiting sodium-hydrogen antiport activity in the eye of a human or animal subject in need of antiport regulation to reduce intraocular pressure. Consequently, the combination of Brandt and Cherksey still fails to render Applicants' invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 94-96, and 102–110, 112, and 113 under 35 U.S.C. §103(a) be reconsidered and reversed, and the case moved to allowance.

In sum, therefore, Applicants believe that all rejections have been overcome, and the application is in condition for allowance. Accordingly, Applicants respectfully ask that the application be moved to allowance at the earliest date possible. Should the Examiner

have any questions or comments regarding Applicants' amendment or response, please contact Applicants' undersigned representative at (215) 772-7550. Please direct all correspondence to the below-listed address. If there are any fees due in connection with the filing of this response, please charge the fees to Deposit Account No. 50-4764.

Respectfully submitted,
Civan *et al.*

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